REMARKS

Applicants filed a paper entitled REQUEST FOR INITIALED COPY OF FORM PTO/SB/08A on August 7, 2004, wherein the Examiner was respectfully requested to return a copy of the Form PTO/SB/08A filed July 11, 2006, with the Examiner's initials in the left column next to each cited publication to indicate that the cited publications were considered and amde of record. Applicants have not received a reply to this request and, therefore, applicants reiterate their request for an initialed copy of the Form PTO/SB/08A filed July 11, 2006.

The July 29, 2003 Office Action included a Notice of References Cited (Form PTO-892) which cited "WO 98/39**532**" to Imanishi et al. This citation is incorrect. The correct citation is "WO 98/39**352**" (see sheet 1 of applicants' Form PTO/SB/08A dated October 31, 2001, wherein WO 98/39352 is cited). The Examiner is respectfully requested to correct the USPTO record accordingly.

The Examiner is respectfully requested to acknowledge applicants' claim for priority under 35 USC 119 and to acknowledge receipt of the certified copy of the priority

document that was filed on August 9, 2001.

The specification was amended hereinabove to correct minor clerical errors. No new matter has been introduced.

The amendments to claims 7 to 9 are supported by exemplified compound numbers 2-233 to 2-248 on pages 46 to 47 of the specification.

Minor editorial revisions were made to claims 70 and 76.

The amendments to claims 109, 110, 113 and 114 concerning "adeninyl," "guaninyl," "cytosinyl" and "5-methylcytosinyl" are supported on page 9, line 29 to page 10, line 21 of the specification.

New claims 115 to 118 are supported in the specification on page 5, lines 22 to 27.

Claims 2 and 4 to 6 were rejected under 35 USC 112, second paragraph, as allegedly being indefinte for the reasons set forth on page 2 of the Office Action.

The position was taken in the Office Action that the term "lower", in the terminology of "lower alkyl" and "lower alkoxy", is a relative term which renders claims 2 and 4 to 6 indefinite.

Applicants respectfully disagree with this position for the following reasons.

The terms "lower alkyl" and "lower alkoxy" are included in the following terminology in claims 2 and 4 to 6:

> "selected from the group consisting of ... methyl groups substituted by from 1 to 3 aryl groups the aryl ring of which is substituted by a substituent selected from the group consisting of **'lower alkyl'** and **'lower alkoxy'**...."

It is respectfully submitted that the following specific examples of lower alkyl groups for R^1 and R^2 on page 6, lines 21 to 25 of the specification define a lower alkyl group as having 1 to 6 carbon atoms:

> "'a lower alkyl group' such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, tert-butyl, n-pentyl, isopentyl, 2-methylbutyl, neopentyl, 1-ethyl-propyl, n-hexyl, isohexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl and 2-ethylbutyl."

It is respectfully submitted that the definition of the lower alkyl group should be the same whether referring to an

alkyl group itself or to an alkyl group connected to an aryl group as a substituent.

Furthermore, page 7, lines 23 to 24 of the specification disclose the following specific lower alkyl groups:

> "an aryl group substituted by a lower alkyl group...such as 2-methylphenyl, 2,6-dimethylphenyl...."

The Examiner's attention is directed to examples of "lower alkoxy" groups that are set forth on page 5, lines 30 to 31, referring to a "lower alkoxy carbonyl group," as follows: methoxy, ethoxy, t-butoxy and isobutoxy. It is respectfully submitted that the lower alkoxy group should be the same whether referring to a lower alkoxy group in the lower alkoxy carbonyl group or an alkoxy group connected to an aryl group as a substituent.

In the paragraph bridging pages 7 and 8 of the specification, alkoxy groups having 1 to 4 carbon atoms for R^3 and R^4 are disclosed. It is respectfully submitted that one of ordinary skill in the art would apply such disclosure to define the lower alkoxy groups recited in claims 2 and 4 to 6.

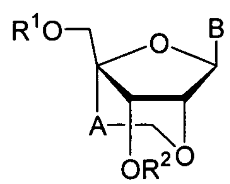
Moreover, the terms "lower alkyl" and "lower alkoxy" with respect to being substituents for an aryl group, which is a

substituent for a methyl group, are refferred to on page 5, lines 25 to 28 of the specification as follows:

> "'a methyl group substituted by from 1 to 3 aryl groups wherein said aryl ring is substituted by a lower alkyl, lower alkoxy...group' such as a 4-methylbenzyl, 2,4,6-trimethylbenzyl, 3,4,5-trimethylbenzyl, 4-methoxybenzyl, 4-methoxy-phenyldiphenylmethyl, 4,4'-dimethoxytriphenylmethyl...."

It is therefore respectfully submitted that the claims comply with all the requirements of 35 USC 112. Withdrawal of the rejection of claims under 35 USC 112, second paragraph is thus respectfully requested.

The present claims are directed to a compound of formula (1):



(1)

wherein:

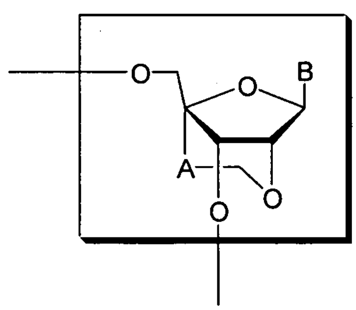
R^1 and R^2 are the same or different and are selected from the group consisting of hydrogen atoms, hydroxyl protecting groups, phosphate groups, protected phosphate groups and a group of formula $-P(R^3)R^4$, wherein R^3 and R^4 are the same or different and are selected from the group consisting of hydroxyl groups, protected hydroxyl groups, mercapto groups, protected mercapto groups, amino groups, alkoxy groups having from 1 to 4 carbon atoms, alkylthio groups having from 1 to 4 carbon atoms, cyanoalkoxy groups having from 1 to 5 carbon atoms and amino groups substituted by an alkyl group having from 1 to 4 carbon atoms;

A represents a methylene group; and

B is selected from the group consisting of unsubstituted purin-9-yl groups, unsubstituted 2-oxo-pyrimidin-1-yl groups, and substituted purin-9-yl groups and substituted 2-oxo-pyrimidin-1-yl groups having at least one substituent α selected from the group consisting of hydroxyl groups, protected hydroxyl groups, alkoxy groups having from 1 to 4 carbon atoms, mercapto groups, protected mercapto groups, alkylthio groups having from 1 to 4

carbon atoms, amino groups, protected amino groups, amino groups substituted by an alkyl group having from 1 to 4 carbon atoms, alkyl groups having from 1 to 4 carbon atoms and halogen atoms; or a salt thereof (see applicants' claim 1).

The present claims are also directed to an oligonucleotide analogue comprising two or more nucleoside units, wherein at least one of said nucleoside units is a structure of the formula (2):



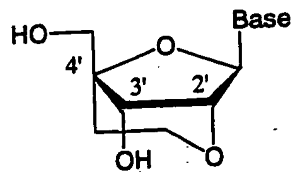
(2)

wherein:

A represents a methylene group; and

B is defined as above (see applicants' claim 62).

The gist of applicants' claims is the following compound:

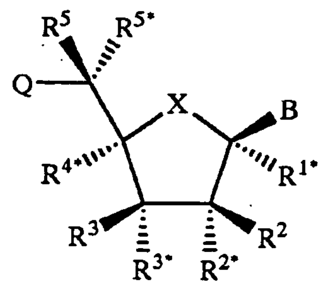


ENA

Claims 1 to 7, 37 to 45, 55, 62 to 65, 70, 72, 76 and 111 were rejected under 35 USC 102 as being anticipated by Wengel et al. (USP 6,794,499) for the reasons set forth in the paragraph bridging pages 3 and 4 of the Office Action.

Wengel et al. have no specific teaching or disclosure of applicants' ENA compounds. There is no specific example in the more than 41 drawings and 194 columns of Wengel et al. for applicants' ENA compounds.

The Office Action refers to the following formula IIA at the top of column 28 of Wengel et al.:



IIa

The Office Action further refers to column 28, lines 17 to 28 of Wengel et al. This is only a portion of the entire paragraph in column 28, lines 17 to 32 of Wengel et al. which is reproduced as follows:

> In a particularly interesting embodiment of the monomeric LNAs of the present invention, B designates a nucleobase, preferably a nucleobase selected from thymine, cytosine, urasil, adenine and guanine (in particular adenine and guanine), X is —O—, R^{2*} and R^{4*} together designate a biradical selected from $—(CH_2)_{0-1}—O—(CH_2)_{1-3}—$, $—(CH_2)_{0-1}—S—(CH_2)_{1-3}—$, and $—(CH_2)_{0-1}—N(R^N)—(CH_2)_{1-3}—$, in particular $—O—CH_2—$, $—S—CH_2—$ and $—R^N—CH_2—$, where R^N is selected from hydrogen and C_{1-4}-alkyl, Q designates Prot-O—, R^{3*} is Q* which designates Act-OH, and R^{1*}, R^2, R^3, R^5, and R^{5*} each designate hydrogen. In this embodiment, R^N may also be selected from DNA intercalators, photochemically active groups, thermochemically active groups, chelating groups, reporter groups and ligands.

To arrive at applicants' claimed compounds from column 28, lines 17 to 28 of Wengel et al., as identified in the Office Action, a person of ordinary skill in the art would have to choose one of three of the following formulae having the following possibilities:

Formula			Total Possibilities
(1) $(CH_2)_{0-1}$ -O- $(CH_2)_{1-3}$			2 x 3 = 6
2 possibilities (0 or 1)	3 possibilities (1, 2 or 3)		
(2) $(CH_2)_{0-1}$ -S- $(CH_2)_{1-3}$			2 x 3 = 6
2 possibilities (0 or 1)	3 possibilities (1, 2 or 3)		
(3) $(CH_2)_{0-1}$	-N(R^N)-	$(CH_2)_{1-3}$	2 X 9 X 3 = 54
2 possibilities (0 or 1)	9 possibilities (R^N is H or C_1-C_4 alkyl, including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl and tert-butyl)*	3 possibilities (1, 2 or 3)	
Total possibilities for formulae (1), (2) and (3) :			**66**

***see column 33, lines 6 et seq. of Wengel et al.**

In the portion of column 28 relied upon in the Office Action, there is thus 66 possible compounds. However, the Office Action neglected to refer to lines 29 to 32 in column 28 of Wengel et al., which describe further possibilities for R^N. Column 28, lines 29 to 32 of this same embodiment state as follows:

> "In this embodiment, R^N may also be selected from DNA intercalators, photochemically active gropus, thermochemically active groups, chelating groups, reporter groups and ligands."

Taking into consideration the many possible groups for R^N as set forth in the preceding paragraph, it is respectfully submitted that column 28, lines 17 to 32 of Wengel et al. disclose thousands or tens of thousands of possibilities. See column 12, line 4 to column 13, line 39 of Wengel et al., which is reproduced as follows:

When used herein, the term "DNA intercalator" means a group which can intercalate into a DNA or RNA helix, duplex or triplex. Examples of functional parts of DNA intercalators are acridines, anthracene, quinones such as anthraquinone, indole, quinoline, isoquinoline, dihydroquinones, anthracyclines, tetracyclines, methylene blue, anthracyclinone, psoralens, coumarins, ethidium-halides, dynemicin, metal complexes such as 1,10-phenanthroline-copper, tris(4,7-diphenyl-1,10-phenanthroline)ruthenium-cobalt-enediynes such as calcheamicin, porphyrins, distamycin, netropcin, viologen, daunomycin. Especially interesting examples are acridines, quinones such as anthraquinone, methylene blue, psoralens, coumarins, and ethidium-halides.

In the present context, the term "photochemically active groups" covers compounds which are able to undergo chemical reactions upon irradiation with light. Illustrative examples of functional groups hereof are quinones, especially 6-methyl-1,4-naphtoquinone, anthraquinone, naphtoquinone, and 1,4-dimethyl-anthraquinone, diazirines, aromatic azides, benzophenones, psoralens, diazo compounds, and diazirino compounds.

In the present context "thermochemically reactive group" is defined as a functional group which is able to undergo thermochemically-induced covalent bond formation with other groups. Illustrative examples of functional parts thermochemically reactive groups are carboxylic acids, carboxylic acid esters such as activated esters, carboxylic acid halides such as acid fluorides, acid chlorides, acid bromide, and acid iodides, carboxylic acid azides, carboxylic acid hydrazides, sulfonic acids, sulfonic acid esters, sulfonic acid halides, semicarbazides, thiosemicarbazides, aldehydes, ketones, primary alkohols, secondary alkohols, tertiary alkohols, phenols, alkyl halides, thiols, disulphides, primary amines, secondary amines, tertiary amines, hydrazines, epoxides, maleimides, and boronic acid derivatives.

In the present context, the term "chelating group" means a molecule that contains more than one binding site and frequently binds to another molecule, atom or ion through more than one binding site at the same time. Examples of functional parts of chelating groups are iminodiacetic acid, nitrilotriacetic acid, ethylenediamine tetraacetic acid (EDTA), aminophosphonic acid, etc.

In the present context, the term "reporter group" means a group which is detectable either by itself or as a part of an detection series. Examples of functional parts of reporter groups are biotin, digoxigenin, fluorescent groups (groups which are able to absorb electromagnetic radiation, e.g. light or X-rays, of a certain wavelength, and which subsequently reemits the energy absorbed as radiation of longer wavelength; illustrative examples are dansyl (5-dimethylamino)-1-naphthalenesulfonyl), DOXYL (N-oxyl-4,4-dimethyloxazolidine), PROXYL (N-oxyl-2,2,5,5-tetramethylpyrrolidine), TEMPO (N-oxyl-2,2,6,6-tetramethylpiperidine), dinitrophenyl, acridines, coumarins, Cy3 and Cy5 (trademarks for Biological Detection Systems, Inc.), erytrosine, coumaric acid, umbelliferone, texas red, rhodamine, tetramethyl rhodamine, Rox, 7-nitrobenzo-2-oxa-1-diazole (NBD), pyrene, fluorescein, Europium, Ruthenium, Samarium, end other rare earth metals), radio-isotopic labels, chemiluminescence labels (labels that are detectable via the emission of light during a chemical reaction), spin labels (a free radical (e.g. substituted organic nitroxides) or other paramagnetic probes (e.g. Cu^{2+}, Mg^{2+}) bound to a biological molecule being detectable by the use of electron spin resonance spectroscopy), enzymes (such as peroxidases, alkaline phosphatases, β-galactosidases, and glycose oxidases), antigens, antibodies, haptens (groups which are able to combine with an antibody, but which cannot initiate an immune response by itself, such as peptides and steroid hormones), carrier systems for cell membrane penetration such as: fatty acid residues, steroid moieties (cholesteryl), vitamin A, vitamin D, vitamin E, folic acid peptides for specific receptors, groups for mediating endocytose, epidermal growth factor (EGF), bradykinin, and platelet derived growth factor (PDGF). Especially interesting examples are biotin, fluorescein, Texas Red, rhodamine, dinitrophenyl, digoxigenin, Ruthenium, Europium, Cy5, Cy3, etc.

In the present context "ligand" means something which binds. Ligands can comprise functional groups such as: aromatic groups (such as benzene, pyridine, naphtalene, anthracene, and phenanthrene), heteroaromatic groups (such as thiophene, furan, tetrahydrofuran, pyridine, dioxane, and pyrimidine), carboxylic acids, carboxylic acid esters, carboxylic acid halides, carboxylic acid azides, carboxylic acid hydrazides, sulfonic acids, sulfonic acid esters, sulfonic acid halides, semicarbazides, thiosemicarbazides, aldehydes, ketones, primary alcohols, secondary alcohols, tertiary alcohols, phenols, alkyl halides, thiols, disulphides, primary amines, secondary amines, tertiary amines, hydrazines, epoxides, maleimides, C_1–C_{20} alkyl groups optionally interrupted or terminated with one or more heteroatoms such as oxygen atoms, nitrogen atoms, and/or sulphur atoms, optionally containing aromatic or mono/polyunsaturated hydrocarbons, polyoxyethylene such as polyethylene glycol, oligo/polyamides such as poly-β-alanine, polyglycine, polylysine, peptides, oligo/polysaccharides, oligo/polyphosphates, toxins, antibiotics, cell poisons, and steroids, and also "affinity ligands", i.e. functional groups or biomolecules that have a specific affinity for sites on particular proteins, antibodies, poly- end oligosaccharides, and other biomolecules.

Moreover, Wengel et al. in column 28, lines 25 to 26 refer particularly to $-O-CH_2-$, $-S-CH_2-$ and $-R^N-CH_2$. This includes at least nine possibilities when R^N is C_1-C_4 or hydrogen (and many more possibilities when R^N is as defined in column 28, lines 29 to 32 of Wengel et al.). None of these preferred possibilities fall within the scope of applicants' claims. Indeed, these particular groups point away from applicants' claims.

When considering the above-described extremely large number of possibilities encompassed in column 28, lines 17 to 32 of Wengel et al., it is respectfully submitted that there is no direction to arrive at applicants' ENA compounds.

Anticipation is not made out by a hindsight selection based on applicants' disclosure of many variables of a broad generic disclosure, such as in Wengel et al. In re Rushig, 145 USPQ 274, 282 (CCPA 1965).

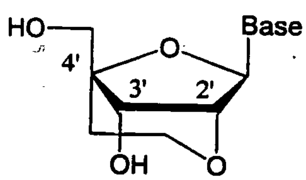
In view of the above, withdrawal of the anticipation rejection is respectfully requested.

Claims 1, 3 to 9, 19 to 27, 37 to 45, 55 to 61, 66, 68, 70, 72, 74, 76, 103 to 110 and 112 to 114 were rejected under 35 USC 103 as being unpatentable over Wengel et al. (USP 6,794,499) for the reasons set forth on pages 4 to 6 of the Office Action.

It was admitted in the Office Action that Wengel et al. do not specifically teach the features like the various substituted bases, specific groups like 2- and 4-chlorophenyl phosphate groups, etc., recited in the instant claims.

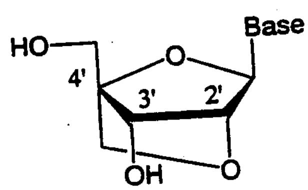
As discussed above, applicants' claims are directed to ENA. As seen in the following structures, it is considered that the closest disclosed compounds in Wengel et al. are (i) LNA(BNA) and (ii) compounds having an ethoxy bridge in the 2- and 3-positions (see Figs. 24 and 25 in Wengel et al.).

Applicants' Claims

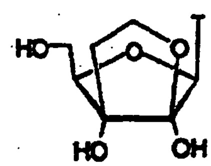


ENA

Wengel et al.



LNA (BNA)



2'-O,3'-C-CH_2CH_2
bridging group
compound 13

The above compound 13 in Fig. 25 of Wengel et al. has the same 2'-O,3'-C-CH_2CH_2 bridge as compound V in Fig. 2 of Wengel et al. Compound V is described in Example 124 of Wengel et al. Some of the inventors of Wengel et al.

published papers on the synthesis and properties of this compound V (Christensen et al., (1998), J. Am. Chem. Soc. 120, 5458-5463 and Nielsen et al., (1997), Chem. Comm. 825-826, copies of which are enclosed).

Compound V contains the same CH_2CH_2 bridging group as the 2'-O,4'-C-CH_2CH_2 bridged nucleic acids. However, in Christensen et al., the authors said that the preferred furanose conformation of compound V has a pseudorotation angle $P = 129°$ corresponding to the C1'-exo conformation. The pseudorotation angle P of the furanose of 2'-O,4'-C-methylene thymidine (an LNA unit) is 16.8° and 14.7° (the cell unit of 2'-O,4'-C-methylene thymidine has two conformers in a crystal structure analysis (Morita et al., (2003), Biorg. Med. Chem., 11, 2211-2226, a copy of which is enclosed). These P values correspond to a typical C3'-endo conformation. The pseudorotation angles P of the furanose of 2'-O,4'-C-methylene adenosine and 2'-O,4'-C-ethylene adenosine are 15.1 and 17.4, respectively, corresponding to the C3'-endo conformation (Morita et al.). These data indicate that two types of nucleosides containing a 2'-O,4'-C-methylene or a 2'-O,4'-C-ethylene bridging group have the similar C3'-endo conformation

and that compound V having a 2'-O,3'-C CH_2CH_2 bridging group has a different conformation from the nucleoside containing a 2'-O,4'-C-ethylene bridging group.

In Table 1 of Christensen et al., melting temperatures of duplexes of oligonucleotides containing compound V units with complementary ssDNA or complementary ssRNA showed that these duplexes were less stable than the unmodified reference duplex. The authors said that "incorporation of one to four modified bicyclic nucleosides X into a 14-mer destabilizes duplexes with the DNA complement dA14 by 2-3°C per modification" (see page 825 in Nielsen et al.). On the other hand, melting temperatures of duplexes of oligonucleotides containing 2'-O,4'-C-ethylene bridging group with complementary ssDNA or complementary ssRNA showed that these duplexes were more stable than the unmodified reference duplexes (Morita et al.).

The melting temperatures of duplexes of oligonucleotides containing 2'-O,4'-C-methylene linkages have improved stability compared to the unmodified reference duplexes (see page 2212, left-hand column, lines 11 to 19 of Morita et al.). It should be further noted from Morita et al. that by contrast with the art,

the nucleosides of the present claims having a 2'-O,4'-C-ethylene linkage give duplexes having even higher levels of stability (see page 2215, left-hand column, lines 11 to 14 of Morita et al.). This could not possibly have been predicted from Wengel et al.

Attention is directed to the following enclosed publications as further evidence of the surprising improvement in properties achieved using the ENA compounds of the present application when compared to the prior art compounds: Obika et al., (2001), Bioorg. Med. Chem., 9, 1001-1011; Koizumi et al., (2003), Nucleic Acids Research, 31, 3267-3273.

In these two publications, there are comparisons concerning the effect on triplex formation of incorporation into oligonucleosides of prior art nucleosides having a 2'-O,4'-C-methylene linkage and nucleosides of the present claims having a 2'-O,4'-C-ethylene linkage. Fully modified LNA oligonucleotides of the prior art did not bind to double-stranded DNA (see Obika et al.), whereas fully modified ENA oligonucleotides of the present claims have a high triplex forming ability (see Koizumi et al.).

The thermodynamic stability of the triplex containing ENA-3, a triplex-forming oligonucleotide (TFO) modified fully with ENA (the melting temperature (T_m) value of ENA-3 was 42°C) was greater than that of a mixture of dsDNA and an oligonucleotide modified fully with LNA, BNA-3, which failed to bind to the dsDNA (see Table 1 in Koizumi et al.). A fully modified TFO, ENA-6, with 5-methylcytosine, instead of cytosine, also showed a much higher T_m value, 57°C, than that of a LNA oligonucleotide (BNA-6: T_m was not detected (see Table 1 in Koizumi et al.).

The binding activity of ENA oligonucleotides to dsDNA by gel analysis was investigated (see Figure 2 in Koizumi et al.). Each TFO was incubated with dsDNA in a ratio of 1:1 or 10:1 for 10 minutes at 60°C. After they were left for 60 minutes at room temperature, they were subjected to 10% PAGE with a neutral buffer at pH 7.2 at 20°C. In a ratio between TFO and dsDNA of 1:1, for fully modified ENA-6 only a faint band indicating triplex formation was observed (see Figure 2A in Koizumi et al.). In a ratio between TFO and dsDNA of 10:1, fully modified ENA-6 formed a triplex. However, the fully modified LNA

oligonucleotide, BNA-6, completely failed to bind to dsDNA (see Figure 2B in Koizumi et al.).

A negative cotton effect was observed at approximately 215 nm in the CD spectra of the triplex. In a ratio between dsDNA and TFO of 1:10, the negative cotton effect was observed at approximately 220 nm in the CD spectra of the complex with a fully modified ENA-6 (see Figure 3B in Koizumi et al.). In the case of a fully modified BNA-6, a negative band was not observed (see Figure 3B in Koizumi et al.).

The selected NF-κB binding sequences have a recognition site that is identified by restriction enzyme *Mln* I (see Figure 1B in Koizumi et al.). If a TFO binds to this recognition site of dsDNA, the *Mln* I reaction would be inhibited. At a pH 7.2, each TFO was incubated with dsDNA in a ratio of 10:1 for 10 minutes at 60°C and left for 5 minutes at room temperature. This was followed by the addition of *Mln* I and incubation was carried out for 1 hour at 37°C. Finally, the resulting mixture was analyzed by denaturing 10% PAGE. Fully modified ENA-6 inhibited *Mln* I cleavage, but fully modified LNA TFO, BNA-6, did not (see Figure 4 in Koizumi et al.).

The above-described results demonstrate that fully modified ENA oligonucleotides can be used as TFOs, as opposed to the fully modified LNA oligonucleotides, which fail to form a triplex, as previously reported in Obika et al. This substantial improvement in triplex-forming ability could not possibly have been predicted from the prior art. It should also be noted that this improvement was demonstrated for oligonucleotides of the present claims having a variety of different bases at the 1'-position.

Enclosed is a copy of Freir et al., (1997), Nucleic Acids Research, 25, 4429-4443, which shows that a 6-membered bridged nucleoside (74) (see page 4434, left column in Table 7 and Figure 3 of Freir et al.) has a low ΔTm. In contrast thereto, the ΔTm of ENA is high. Based on the teaching of Freir et al., it is respectfully submitted that one of ordinary skill in the art would have expected that the ΔTm of ENA was also low and therefore would not have attempted to make ENA.

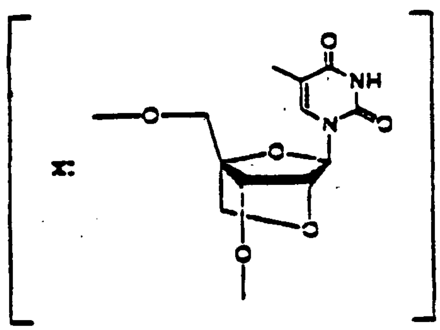
With respect to BNA disclosed in Wengel et al., of record is a DECLARATION UNDER 37 CFR 1.132 of Dr. Makoto KOIZUMI dated September 2, 2003, which provides a showing of unexpected results

for the present claims (ENA) over BNA, i.e., a 2'-O,4'-O-methylene nucleoside.

The September 2, 2003 KOIZUMI DECLARATION includes comparison test results for the following compounds.

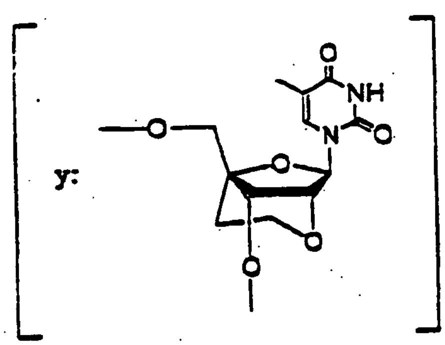
Oligonucleotide A which contains the 2'-O,4'-C-methylene nucleoside:

Oligonucleotide A: 5'-ttt ttt ttt txt-3'



Oligonucleotide B according to the present claims:

Oligonucleotide B: 5'-ttt ttt ttt tyt-3'



The resistance of each of oligonucleotide A and oligonucleotide B was tested against snake venom phosphodiesterase according to the method of Test Example 2 of the present specification. The rsults are shown in Table 1 of the September 2, 2003 KOIZUMI DECLARATION, which is reproduced as follows:

Table 1. Percentage of remaining oligonucleotides.

Sample	0 min	30 min	120 min
Oligonucleotide A	100	15	not detected
Oligonucleotide B (according to the present claims)	100	90	82

The above results show that whereas oligonucleotide A was no longer detected after 120 minutes of incubation, 82% of

oligonucleotide B according to the present claims still remained. Oligonucleotide B of the present claims has an unexpectedly much higher nuclease resistance activity than oligonucleotide A. It is respectfully submitted that the remarkably high nuclease resistance activity of the compounds of the present claims is an unexpected result which would not have been expected.

Submitted herewith is a DECLARATION UNDER 37 CFR 1.132 of Dr. Makoto KOIZUMI dated November 6, 2006, having attached thereto Certificates of Experimental Results (2), (3), (5) and (6) that were submitted in the corresponding European patent application and relate to issues raised in said European patent application. The results set forth in said attachments show unexpected results for oligonucleotides containing ENA of the present claims compared to oligonucleotides containing BNA such as in Wengel et al.

In view of the above, withdrawal of the obviousness rejection is respectfully requested.

It is therefore respectfully submitted that applicants' claims are not anticipated or rendered obvious by the reference.

Reconsideration is requested. Allowance is solicited.

An INFORMATION DISCLOSURE STATEMENT is being filed concomitantly herewith.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,

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RSB/ddf

Encs.: (1) PETITION FOR EXTENSION OF TIME

(2) DECLARATION UNDER 37 CFR 1.132 of Dr. Makoto KOIZUMI dated November 6, 2006

(3) a copy of Christensen et al., (1998), J. Am. Chem. Soc., 120, 5458-5463.

(4) a copy of Nielsen et al. (1997), Chem Comm., 825-826.

(5) a copy of Morita et al., (2003), Bioorg. Med. Chem., 11, 2211-2226.

(6) a copy of Obika et al., (2001), Bioorg. Med. Chem., 9, 1001-1011.

(7) a copy of Koizumi et al., (2003) Nucleic Acids Research, 31, 3267-3273.

(8) a copy of Freier et al., (1997), Nucleic Acids Research, 25, 4429-4443.

(9) INFORMATION DISCLOSURE STATEMENT